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NOTES ON MALARIA IN THE TREATMENT OF GENERAL PARALYSIS OF THE INSANE*

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MALARIA is now of interest to others than tropical practitioners, and especially so to syphilologists. The *Wagner-Juaregg treatment* of G.P.I. and tabes dorsalis by inducing a malarial infection and a sequential series of fever paroxysms is now well known, and its apparent therapeutic effect is still admitted.

Although its anti-syphilitic effect on the patient is of prime interest, and all the more so because still unexplained, that effect is not considered here. These notes deal only with the malaria as a therapeutic agent, with the methods of employing it, and with its dangers.

In 1900 Manson carried out the crucial experiment of infecting with malaria (*Plasmodium vivax*) two healthy patients, in London, by the bites of anopheline mosquitoes brought from Rome, where they had been fed on a malarial subject. Since then further direct experimental study of human malaria has had to wait for the opportunity now afforded by the malaria treatment of G.P.I. This recent experimental study has disclosed facts which are of importance in malariology and cogent for those attempting this method of treating central nerve parenchyma syphilis.

(1) THE PLASMODIUM SPECIES

P. malariae (quartan) has been but little tried.

P. falciparum (malignant or sub-tertian) has proved to be comparatively ineffective therapeutically, and, not unexpectedly, to be highly dangerous. When present (and not recognised in time) with *P. vivax*, and when deliberately used alone with what was thought to be the sufficient safeguard of daily blood examinations, it has

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killed some patients by the production of sudden fulminating cerebral malaria.

P. vivax (benign tertian) is less dangerous than *P. falciparum*, gives usually severer fever paroxysms, has apparently a higher therapeutic value, and is therefore the species of choice.

Before using a strain of *P. vivax* it is essential to be sure by repeated blood examinations that it is pure. The danger of overlooking a mixture with *P. falciparum* has been already noted. Once a pure strain be obtained, it has been found to retain its morphological and biological characters during years, and repeated passages, however transmitted, through the human being. The hypothesis of the "unicity" of the different species of human plasmodia has thus been finally disproved by experiment. Any strain, if observed for long enough, shows no real change in virulence.

(2) METHODS OF INDUCING MALARIA

(a) *By subcutaneous, intramuscular, or intravenous injection of blood containing malarial parasites.*

Some of these parasites must be trophozoites (a-sexual). Injection of blood containing gametocytes (sexual) only has failed to produce infection. "Parthenogenesis" of malarial parasites therefore does not occur.

The incubation period of these trophozoite-injected cases has varied from five to thirty-one days—though a strain may show a great constancy of incubation period in too human passages. The incubation period has differed with the tissue-site of injection; thus it may be from four to eight days for intravenous, six to thirty-one days for subcutaneous injection; and ten to sixteen days for dermal (scarification); but any two patients inoculated at the same time, in corresponding tissue-sites, with the same quantity of the same blood, may show different incubation periods.

Injection of *P. vivax* blood has often failed to produce evident malaria. Sometimes this failure has been apparent only—the infection was real but latent. Most patients became infected on repeating the injection. Repeated failure is more likely in those who have previously had malaria.

(b) *By the bites of mosquitoes, usually Anopheles maculipennis, or A. bifurcatus, previously infected by*

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being fed on malaria cases showing gametocytes in the peripheral blood.

The infection is here received as sporozoites. The incubation period has varied from twelve to twenty-one days. Failure of infective *A. maculipennis* to produce malarial infection of the patient may, however, occur, and here again failure to infect is more likely to occur in those who have previously suffered from malaria. (This most important matter of immunity is to be further investigated.)

THE MALARIAL INFECTION IN THE PARALYTIC

Even with the same strain of *P. vivax*, injected or mosquito-transmitted, different patients may show very different malarial syndromes.

It has been shown that in *P. vivax* infection the red blood corpuscles increase 10 to 30 per cent. before fever appears.

Usually, with *P. vivax* infection, the fever begins irregularly remittent in form. It may be several days before it changes to the intermittent type, and then the fever is quotidian—rarely of the tertian type usually seen in long-standing ("established") infections.

Fever and parasites may disappear spontaneously. Once more, this is more likely to occur if the patient has previously had malaria.

In one *P. vivax*-injected case of the writer's, after spontaneous disappearance of fever, and of parasites from the cutaneous blood, for a period of three days, both returned, the fever paroxysms being more severe than at first.

Fever may be low or very high. In one case of the writer's (*P. vivax* mosquito-sporozoite infection) the temperature reached 107° F.

Deaths during *P. vivax* infection have been recorded. It is therefore essential to examine the blood daily. A large increase in the number of parasites indicates danger. But there may be real danger even with low fever, and few parasites in the cutaneous blood. One of the writer's cases died rapidly during the fifth fever paroxysm, when the temperature had never reached 103° F., and *P. vivax* parasites, two hours before death, had been found to be comparatively few in the peripheral blood. Yet another of his cases became semi-comatose

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with temperature 106° F., at the same time showing comparatively few of the *P. vivax* parasites in the cutaneous blood. It is, therefore, not enough to rely for warning solely on temperature chart and blood examination.

A continuous clinical watch on the patient is necessary. (The patient is damaged, obviously, by his syphilis before he receives the malaria.)

SELECTION OF PATIENT TO BE MALARIALY INFECTED.

The records show clearly that the more recent the spirochete invasion of the central nerve parenchyma, the better the results of treatment. For the rest, the poorer the physical condition of the patient, the more dangerous the treatment. It may perhaps be postulated that the recorded beneficial results of the treatment justify its risk except for the almost moribund—for syphilis of the central nervous parenchyma is relentless.

STOPPING THE FEVER AND CURING THE MALARIA

The best results have followed on a run of ten to twelve fever paroxysms. Usually quinine stops, not the next fever paroxysm, but the next but one. Allowance for this must be made in deciding on the number of further paroxysms to be allowed to any one patient before administering quinine.

Intravenous injection of quinine may be kept for comatose cases, but with *P. vivax* infections, carefully watched, its need should not arise.

Intramuscular, or subcutaneous, quinine injection is painful and even dangerous, and has no advantage over quinine in solution taken by mouth.

Disinfestation has proved surprisingly easy for *injected trophozoite* infections. Three to ten grams of quinine have brought about cure. Not more than 3 per cent. of relapses have been noted after this small amount of quinine. The quinine salt selected makes no difference. In contrast, mosquito-sporozoite infections have shown 57 per cent. relapses after the same quinine dosage.

Even this 57 per cent. of relapses is notably smaller than that usually experienced for malaria naturally acquired in malarial regions. This experimental study brings out clearly the importance of adequate treatment of malaria as soon as possible after infection ; and that

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the host is an important factor in determining the course and type of the malaria syndrome. The analogy with syphilis is close.

Arseno-benzol compounds have been used in the treatment of malaria. The writer, with others, has observed the onset of fever and the appearance of *P. vivax* or *P. falciparum* in the cutaneous blood of some patients (former malarial subjects) who were being given injection courses of arseno-benzol and bismuth or mercury. These were "established" cases of malaria and syphilis.

It is therefore of interest to note the record that after injection of *P. vivax* into G.P.I. patients the fever can be cut out by injection of neo-salvarsan. These are not "established" cases of malaria.

SELECTION OF THE METHOD OF MALARIAL INFECTION

Infection received as trophozoites obviously reacts to quinine therapy very differently from that acquired as sporozoites, and the therapeutic results are the same for both.

But before deciding that injected-trophozoite infection is always the method of choice, other considerations must be taken into account.

Thus the relatives of one of the writer's cases decidedly objected to their sick one's being injected with "unknown" blood. This objection might easily have been stronger—for later, after the lay Press had found copy in "the malaria treatment of brain syphilis," and concerning another patient who had not benefited, but rather the reverse, from his malaria, his relative repudiated with pain the suggestion that this patient had ever had syphilis, and enquired, threateningly, whether the patient's worsened condition were not due to the writer's having injected him with insane syphilitic blood. (It may have been fancy only that detected disappointment following the proof that the malaria had been mosquito-given.) It is, then, perhaps more worldly-wise for the doctor to use mosquito-sporozoite infection, and easier than finding a certificate of the trophozoite-donor's moral and physical worth.

THE ACTION OF QUININE IN MALARIA

Indirect epidemiological experiment has shown that quinine, gr. 5, given daily over a long period of time, will

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not prevent infection of healthy men with *P. falciparum*, mosquito-transmitted.

Direct experiment with *P. vivax* transmitted by mosquito to G.P.I. patients has shown that 10 gr. quinine taken daily for five days before and seven days after the infective mosquito bites fail to prevent infection. This quantity of quinine must be taken for ten days after the infective mosquito bites in order to prevent infection.

Therefore, *unless taken in "curative" doses*, and for "curative" time, quinine is ineffective against the sporozoite, and is of no prophylactic value.

It has been shown that a G.P.I. patient may be infected by injection of malarial parasites-in-blood-containing-quinine-hydrochlor. 1 in 10,000-for-twelve-hours, and 1 in 5,000-for-five-hours; and that quinine given to a trophozoite-donor does not prevent his blood infecting with malaria a G.P.I. patient.

A. maculipennis has been infected, in winter, with *P. vivax* by feeding on a malarial subject taking quinine.

Quinine has failed to destroy malarial parasites when incubated with blood at body temperature, and in a strength in excess of any hitherto found *in vivo*.

It is clear that quinine given to the host has no direct action on the malarial parasites infesting him.

No strain of *P. vivax* has proved "quinine-resistant," whether previously brought into contact with quinine or not.

These are the facts of direct, controlled experiment with quinine and plasmodia. Speculation as to their meaning is, of course, not lacking, and there is here a certain analogy with *Sp. pallidum*.

It has been noted that gangrene of toes supervening on malaria-injection into a tabetic, and, in another case, malarial amblyopia, disappeared after quinine administration.

IS THE MALARIA-INFECTED PARALYTIC MALARIALY DANGEROUS TO OTHERS ?

With *P. vivax* infections, whether trophozoite-injected or sporozoite-mosquito transmitted, all patients eventually show gametocytes in the cutaneous blood. Usually they appear early, and sometimes *before* the trophozoites. There is, therefore, no ground for the hypothesis that the

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appearance of gametocytes indicates relapse, although they are usually more frequent in relapse.

It is recorded, however, that one strain ran through twenty human passages in two years before showing gametocytes; and another has shown no gametocytes for two years and many human passages, although they were present in the earlier passages. Gametocytes present in the thirty-fifth and forty-first injected human passage, exflagellated, and developed into oocysts in *A. maculipennis*.

All three species of human malarial parasite transmitted by trophozoite-injection have formed gametocytes which readily exflagellated after the fortieth direct transfer.

The G.P.I. patient with "induced." malaria may therefore infect free *Anopheles*. This mosquito is not rare in England.

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